CANCERS of OROPHARYNX and HYPOPHARYNX

STAGING and TREATMENT

1. Staging
2. General Principles of Treatment
3. Site Specific Treatment Guidelines
4. Selected Abstracts from Relevant Studies

1. Staging - AJCC 7th Ed., 2010

OROPHARYNX

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor 2 cm or less in greatest dimension

T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension

T3: Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis

T4a: Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible

T4b: Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

HYPOPHARYNX

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension

T2: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm, but not more than 4 cm in greatest dimension without fixation of hemilarynx

T3: Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus

T4a: Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue

T4b: Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0; No regional lymph node metastasis

N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b: Metastasis in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension

N2c: Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension

N3: Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant metastasis (M)

M0: No distant metastasis

M1: Distant metastasis

STAGE GROUPING

0: Tis N0 M0

I: T1 N0 M0

II: T2 N0 M0

III: T3 N0 M0 ; T1-T3 N1 M0

IVA: T4a N0 M0 ; T4a N1 M0 ; T1-T3 N2 M0
T4a N2 M0

IVB: T4b Any N M0 ; Any T N3 M0

IVC: Any T Any N M1

2. General Principles of Treatment

Goals of Treatment

Stage I - IVA	Curative
Stage IVB - IVC	Palliative

Treatment Modalities

Surgery and Radiotherapy are the definitive therapies in the treatment of HNSCC

Chemotherapy by itself is not a definitive treatment

Surgery

Used as a single modality in early stage disease (I & II)

Preferred over Radiotherapy as a single modality in

i) Sites where surgery is not morbid – cosmetically and functionally

ii) Lesions involving or close to bone – to prevent radionecrosis

iii) Young patients – possibility of a subsequent second primary

iv) Sub-mucous fibrosis

Advantages of Surgery compared to Radiotherapy

i) Exact histopathological diagnosis and anatomical extent determined

ii) Treatment time is shorter

iii) Limited amount of tissue exposed to treatment

iv) No radiation related complication

Used as a part of combined modality treatment along with Radiotherapy in advanced stage disease (III & IV)

Rationale for combined modality treatment

Surgery is effective in removing large bulky lesion

Radiotherapy takes care of microscopic disease

Radiotherapy

Used as a single modality in early stage disease(I & II)

Preferred over surgery as a single modality where

i) Severe impairment of function/cosmesis with surgery
ii) Surgery is technically difficult with high morbidity and poor results
iii) Patient refuses surgery or there is high risk for surgery

Used as part of combined modality along with surgery (with or without chemotherapy) in advanced stage disease (III & IV)

Either pre-operative or post-operative irradiation based therapy may be used – there are advocates of each

Pr-operative Radiation Therapy considered in following -

i) fixed neck nodes
ii) if initiation of post-operative radiotherapy will be delayed by > 8 weeks due to reconstruction
iii) open biopsy of a positive node

Advantages of Pre operative Radiotherapy

i) Inoperable lesions may be converted to operable lesions
ii) Extent of surgery may be decreased
iii) Blood supply at the time of Radiotherapy is intact
iv) Distant metastasis may decrease

Disadvantages of Pre-operative Radiotherapy

i) Increased morbidity

ii) Decreased wound healing

iii) Surgery is difficult as anatomy is not identified

Post-operative Radiation Therapy is indicated in –

Primary-i) Large primary-T3 or T4

ii) Close (<5mm) or positive margins of excision

iii) Deep infiltrative tumor

iv) Lymphovascular and Perineural invasion

Lymph Nodes-i) Bulky nodal disease N2 /N3

ii) Extra nodal extension

iii) Multiple level involvement

Advantages of Post-operative Radiotherapy

i) Extent of the disease is known
ii) Higher doses may be delivered
iii) Wound healing is better

Disadvantages of Post-operative Radiotherapy

i) Distant metastasis is likely to be greater
ii) Decreased vascularity at the time of Radiotherapy due to surgical tampering

Role of Brachytherapy

Interstitial implants selectively used in

i) Accesssible lesions

ii) Small (preferably <3cm) tumors

iii) Lesions away from bone

iv) N0 nodal status

v) Superficial lesions

Chemotherapy

Established role of Chemotherapy as part of the standard combined modality management of HNSCC in –

i) therapy of unresectable disease
ii) for organ preservation
iii) for patients with poor risk pathologic features after surgery

Integrated with Surgery/Radiotherapy as

Induction/ Neo adjuvant therapy
Concurrent with Radiation
Adjuvant/ Maintenance therapy

Current evidence supports concurrent therapy along with radiotherapy as the most efficacious modality

Agents used- platin plus 5-flourouracil
other polychemotherapy without platin
monotherapy with platin
other monotherapy

Platinum based chemotherapy associated with largest benefit – platin plus 5-flourouracil compared to platin alone offers no advantage

A newly available option is Cetuximab and concurrent irradiation – associated with superior results compared to Radiotherapy alone

Rehabilitation

i) Abstinence from tobacco/alcohol
ii) Oral hygeine
iii) Shoulder physiotherapy in all cases of neck dissection
iv) Bite guide prosthesis following mandibulectomy
v) Jaw stretching exercises to prevent post-operative trismus
vi) Speech and Swallowing Rehabilitation

Follow up

Every 2 to 3 months for first two years
6 monthly for next three years
Annually thereafter
On every follow up - thorough head and neck examination for locoregional control, second primary tumor and late sequelae of treatment
Investigation only if indicated by symptoms and positive clinical findings
Serum T3,T4,TSH annually

3. Site Specific Treatment Guidelines

OROPHARYNX

T1-2N0	■ Definitive RT. Alternative, surgery with post-op RT as indicated
III–IV	■ Concurrent chemo-RT (preferred). ■ Alternative, surgery with post-op (chemo-)RT as indicated. For patients not considered candidates for standard chemo-RT (e.g., with cisplatin), consider RT and cetuximab. ■ If unable to tolerate concurrent chemo, altered fractionation RT may be used

Surgery

For early cancers of Tonsillar pillars trans-oral wide local excision including a tonsillectomy can be done; T3-4 Tonsillar lesions require radical tonsillectomy often with partial mandibulectomy & ipsilateral neck dissection.

Base of tongue lesions require partial or total glossectomy and myocutaneous flap reconstruction.

For locally advanced oropharyngeal cancers, primary organ preservation approach with radiation or chemo-RT is preferred.

Types of Neck Dissection

Radical neck dissection (RND) removes levels I–V, Sternocleidomastoid muscle, omohyoid muscle, internal and external jugular veins, CN XI, and the submandibular gland.

Modified RND leaves one or more of sternocleidomastoid muscle, internal jugular vein, or CN XI.

Supraomohyoid neck dissection only removes levels I–III.

Lateral neck dissection only removes levels II–IV.

Radiotherapy

Simulate patient supine with head hyperextended.
Shoulders may be pulled down with straps.
Immobilize with a thermoplastic head and shoulder mask.

Conventional volumes cover the skull base and mastoid to the supraclavicular nodes with a three-field technique (opposed laterals matched to AP lower neck field).
Beam-split above larynx at thyroid notch, if possible, to allow laryngeal sparing.

The anterior margin is set up by clinical examination with at least a 2-cm margin beyond any clinical evidence of disease. This margin should project 2 to 3 cm forward of the anterior cortex of the ramus of the mandible, depending on tumor extent.

Inferiorly,the portal extends to the thyroid notch, except in patients with downward tumor extension with pharyngeal wall involvement; in these cases, the margin must be placed below that level.

Posteriorly, the posterior cervical lymph nodes should be covered.

After a tumor dose of approximately 40 to 45 Gy, the posterior margin of the lateral portal is brought anteriorly to the midportion of the vertebral bodies to spare the spinal cord.

Electrons (12 to 20 MeV) can be used to boost the dose to the primary tumor or large cervical lymph nodes. If necessary, the posterior cervical nodes are irradiated with 9-12 MeV electrons to avoid higher doses to the spinal cord when higher-energy electrons are used.

After 40 to 45 Gy with low-energy megavoltage beams, the remaining dose may be delivered with high-energy x-rays to concentrate the dose centrally and reduce the dose to the parotids, mandible, and temporomandibular joints.

After 60 Gy, the fields are reduced to encompass only the primary tumor and may be weighted to the side involved by tumor.
The boost dose after 60 Gy may be delivered by a submental electron beam or low energy photon beam field.

The lower neck is treated with a standard anteroposterior portal.
If no palpable lymph nodes are present, a 1.5- to 2.0-cm-wide midline block can be used to shield the larynx and spinal cord. If lymph nodes are involved in this area, only a small block is used to shield the larynx and a portion of spinal cord (to avoid overlap with lateral portals).

One technique for treating small tumors of the tonsillar fossa, anterior tonsillar pillar, and retromolar trigone uses ipsilateral wedged-angle anterior and posterior fields that irradiate a triangular volume, with the base on the neck and the apex in the uvula.

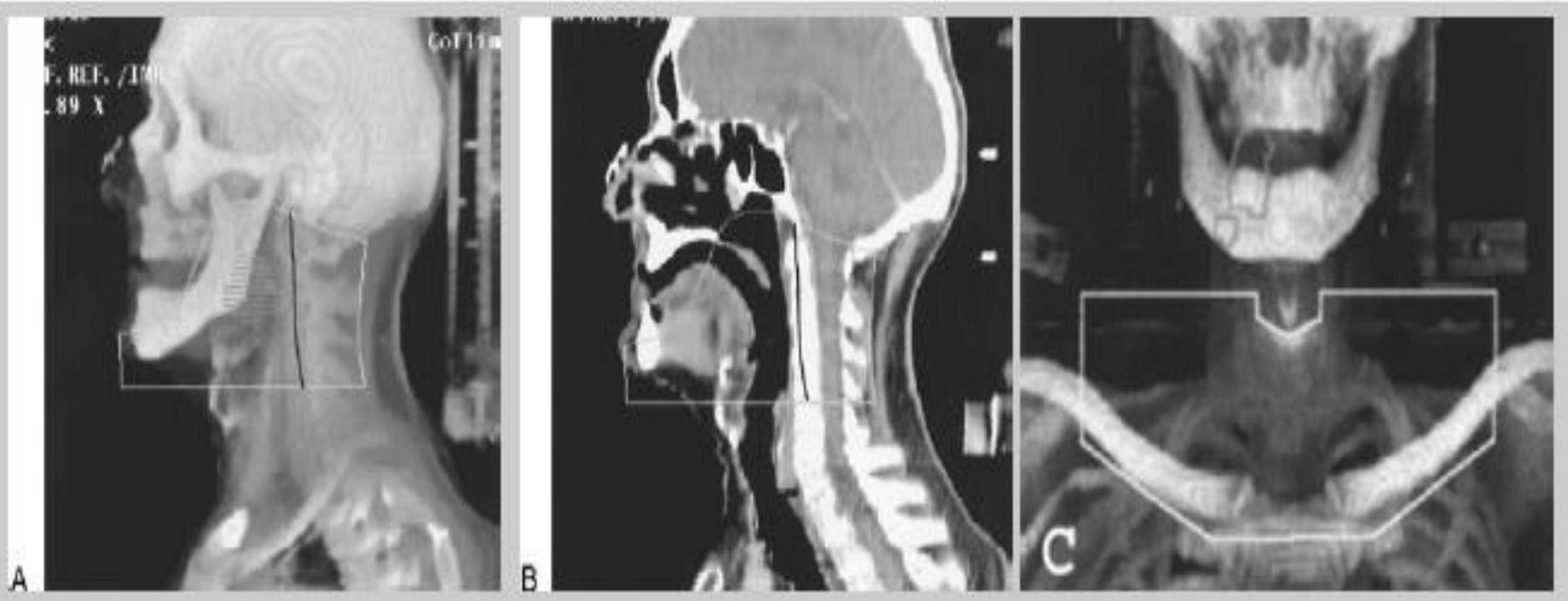
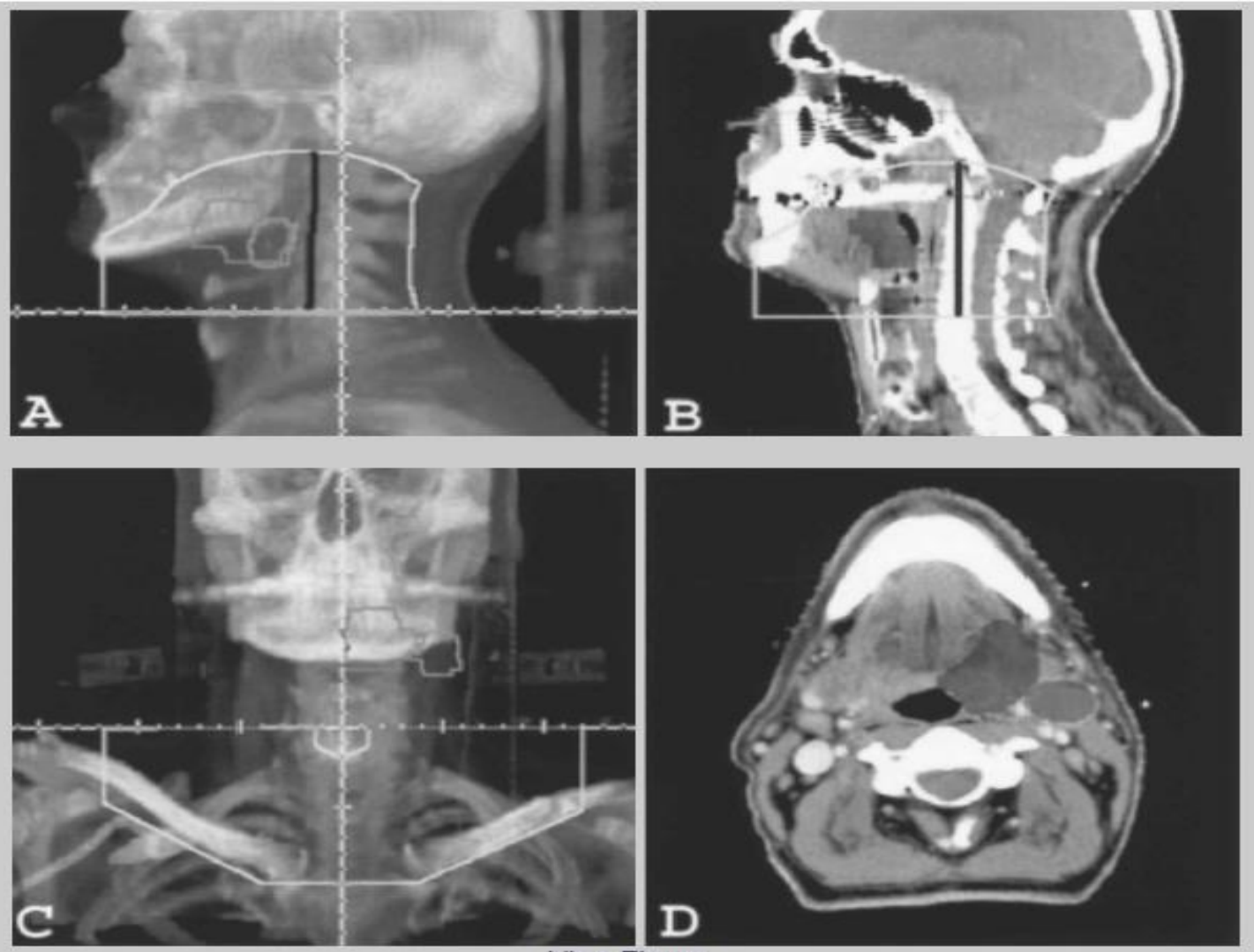


Fig. 24-2: A: A digital composite radiography shows a left lateral portal encompassing a T2N2cM0 squamous cell carcinoma of right tonsil metastasized to level IB node on the right and level II node on the left neck. **B:** A sagittal view shows structures included in the irradiated field. The portals are reduced after 40 to 45 Gy to exclude spinal cord (*dark line*). Tumor boost portal can be designed based on the outlined gross tumor volume. **C:** Anterior lower neck portal.



View Figure

Fig. 25-3: A: A digital composite radiography showing a left lateral portal encompassing a T2N1M0 base of tongue carcinoma. **B:** A sagittal view showing structures included within the irradiated field. The portals are reduced after 40 to 45 Gy to exclude spinal cord (*dark line*). Tumor boost portal can be designed based on the outlined gross tumor volume. **C:** Anterior lower neck portal. **D:** An axial view through the central region of the tumor showing the extension of the primary tumor and the metastatic node.

Dose Prescription

Select T1-2N0 patients:

Definitive conventional fx RT to 70 Gy at 2 Gy/fx.

Select T1N1 and T2N0-1 patients:

Definitive altered-fx RT.

i) Six fx/week during weeks 2–6: 70 Gy at 2 Gy/fx to primary and gross adenopathy.

ii) Concomitant boost: 72 Gy in 6 weeks (1.8 Gy/fx large field;1.5 Gy boost as second daily fx during last 12 treatment days).

iii) Hyperfractionation: 81.6 Gy in 7 weeks at 1.2 Gy b.i.d.

Stage III–IV patients:

Concurrent chemo-RT.

Total dose typically 70 Gy in daily 2 Gy fx with cisplatin 100 mg/m2 q3 weeks × 3c.

Elective neck:

Uninvolved nodal stations: 50–56 Gy at 1.6–2Gy/fx.

Post-op RT:

60–66 Gy at 2 Gy/fx to high-risk areas and the postoperative bed.

Concurrent single agent cisplatin 100 mg/m2 q3 weeks recommended.

Dose Limitations

Spinal cord <45 Gy
Brainstem <54 Gy
Parotid glands Mean dose <26 Gy and/or attempt to keep 50% volume of each parotid <20 Gy (ifpossible)
Mandible <70 Gy
Larynx mean dose <43.5 Gy

Treatment Recommendations for Neck Nodes

Clinically negative neck:

If risk of occult metastasis exists

Surgery for primary with elective neck dissection

(a) If N0, follow

(b) If N1 with no extracapsular extension (ECE), follow

(c) If >pN1 and/or ECE, postoperative RT or chemo-RT

Alternatively, RT or chemo-RT for primary with elective neck RT; surgery for persistent disease

Clinically positive neck:

i) N1

Surgery for primary with selective or modified radical neck dissection
(a) If pN0, follow
(b) If pN1 with no ECE, follow
(c) If >pN1 and/or ECE, postoperative RT or chemo-RT

Alternatively, RT or chemo-RT for primary and involved Neck with elective neck RT; surgery and/or neck dissection for persistent disease

ii) >N1

Surgery for primary with modified radical or radical neck dissection
(a) If pN1 with no ECE, follow
(b) If >pN1 and/or ECE, postoperative RT or chemo-RT

Alternatively, RT or chemo-RT for primary with comprehensive RT for neck ; surgery and/or neck dissection for persistent disease and/or node >3 cm

HYPOPHARYNX

The best treatment for hypopharyngeal carcinoma aims for the highest locoregional control rate with the least functional damage.

Functions that need to be preserved include respiration, deglutition, and phonation. This should be done with the least risk to the host and, if possible, without the use of permanent prosthetic devices.

Early T1-2 not requiring total laryngectomy (T1N0-1, small T2N0, T1N2)	■ Definitive RT. If < complete response, salvage surgery and neck dissection as indicated. If complete response, neck dissection considered for N2-3 ■ Alternatively, partial laryngopharyngectomy and ipsilateral or bilateral selective neck dissection (N0) or comprehensive neck dissection (N+). Post-op chemo-RT for + margin or nodal ECE. Post-op RT (or chemo-RT if multiple factors) for pN2-3, close margin, PNI, LVSI, cartilage invasion

T2-4N0/+ requiring total laryngectomy	■ Concurrent chemo-RT as extrapolated from RTOG 91–11. Or, induction chemo ×2c (with a third cycle if PR). If CR at primary site, proceed with definitive RT (≥70 Gy). If primary site has only PR, proceed with concurrent chemo-RT. Nonresponders to induction chemo should undergo surgery → post-op RT or chemo-RT as indicated. If residual neck mass after definitive RT or initial N2-3, post-RT neck dissection considered ■ Or, laryngopharyngectomy and selective (N0) or comprehensive neck dissection (N+ or T4). Post-op chemo-RT for + margin or nodal ECE. Post-op RT (or chemo-RT if multiple factors) for pT3-4, pN2-3, close margin, PNI, LVSI, cartilage invasion
Unresectable T3-4 or N+	■ Concurrent chemo-RT. If unable to tolerate chemo, definitive RT with CB

Surgery

Total laryngectomy

Indicated for advanced lesions with transglottic or extensive subglottic extension, most pyriform sinus lesions, and/or cartilage invasion

Removes hyoid, thyroid, and cricoid cartilages, epiglottis, strap muscles. Patient left with a permanent tracheostoma and pharynx reconstruction (by suturing to the base of tongue)

Partial laryngopharyngectomy

Used for small medial and anterior pyriform sinus lesions Removes false cords, epiglottis, aryepiglotticfold, and pyriform sinus, but TVCs are preserved

Contraindicated if transglottic extension, cartilage invasion, vocal fold paralysis, pyriform apex invasion (b/c below level of TVCs) postcricoid invasion, exolaryngeal spread, or poor pulmonary reserve

Total laryngopharyngectomy

For more advanced hypopharyngeal lesions

TL plus removal of varying amount of pharyngeal wall

Radiation

Simulate the patient supine with the head hyperextended. Shoulders may be pulled down with straps.
Immobilize with a thermoplastic head and shoulder mask.

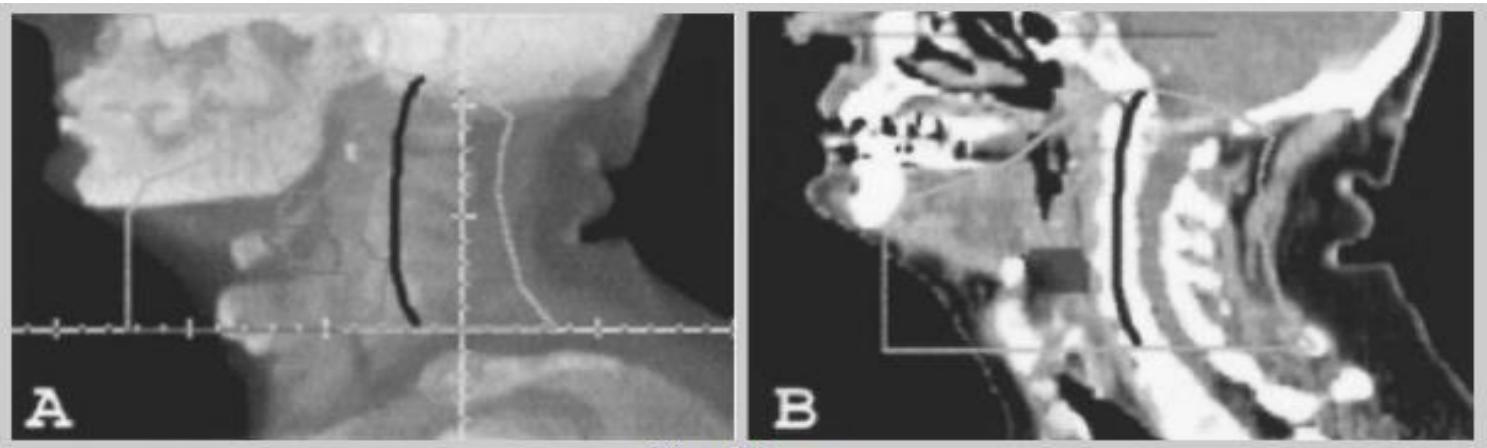
Treat primary and levels II–V and retropharyngeal nodes in all cases.
With traditional field design, the superior border is the skull base and mastoid.
The inferior border is 1 cm below the inferior extent of disease (or 1 cm below cricoid) on the laterals and matched to the AP low-neck field.

Post-operative Radiation

With traditional fields, use 3-field technique with stoma in low-neck AP field. Lateral fields cover neopharynx, adenopathy, and 1.5–2 cm margin on preoperative extent of disease.

With conventional three-field techniques, the spinal cord is shielded on the lateral fields at the matchline if no gross disease is present. If gross disease is present at the matchline, angling the lateral fields to match the divergence of the AP field may help.

A small midline block on the AP field may be necessary.



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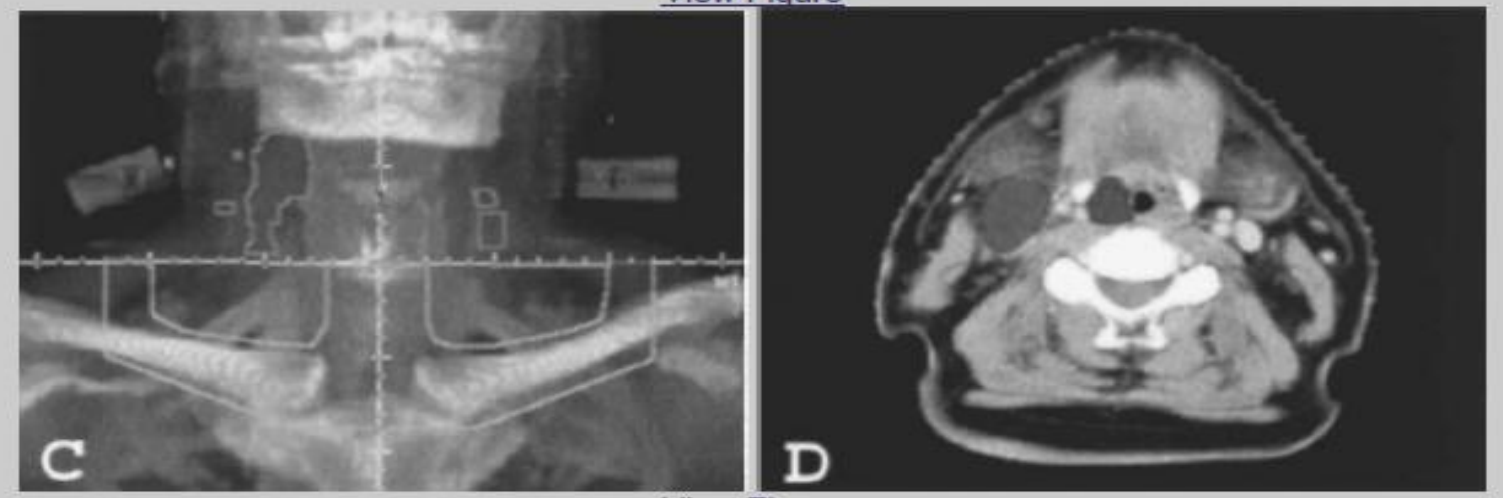

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Fig. 26-4: A: A digital composite radiography showing a left lateral portal encompassing a T2N2CM0 squamous cell carcinoma of the pyriform sinus with bilateral neck nodes metastasis. **B:** A sagittal view showing structures included within the irradiated field. The portals are reduced after 40 to 45 Gy to exclude spinal cord (*dark line*). Tumor-boost portal can be designed based on the outlined gross tumor volume. **C:** Initial anterior lower neck portal for 46 Gy. Off-cord boost to both lower necks will bring total dose to 60 Gy. A beam splitter is used to prevent beam divergence. Moving junction technique may be used since no spinal cord notch is in place due to the tumor extension. **D:** An axial view through the central region of tumor shows the extension of disease and metastatic nodes.

Dose Prescription

T1-2N0 : >2 Gy/fx preferred. If 2 Gy/fx is used, total dose >66 Gy.

T3-4 and LN+ patients:
Concurrent chemo-RT
Total dose typically 70 Gy in daily 2 Gy/fx with cisplatin 100 mg/m2 q3 weeks ×3c.

With definitive RT, use altered fractionation:

i) Six fx/week during weeks 2-6: 70 Gy at 2 Gy/fx to primary and gross adenopathy.

ii) CB: 72 Gy in 6 weeks (1.8 Gy/fx large field; 1.5 Gy boost as second daily fx during last 12 treatment days).

iii) Hyperfractionation: 81.6 Gy in 7 weeks at 1.2 Gy b.i.d.

4. Abstracts from Selected Studies

1. Pre-op vs. post-op RT

RTOG 73-03 (Kramer et al. 1987; Tupchong et al. 1991):

354 patients with advanced H&N cancer randomized to 2/50 Gy pre-op vs. 2/50/60 Gy post-op.

Post-op RT improved LRC (48→65%), and OS for oropharynx lesions (26→38%).

Complications not different.

2. Altered Fractionation

RTOG 90-03 (Fu et al. 2000,Update ASTRO 2005):
268 patients with locally advanced H&N cancer randomized to 2/70 Gy vs. 1.2 b.i.d./81.6 Gy vs. split-course 1.6 b.i.d./67.2 Gy (with a 2 weeks break) vs. concomitant boost RT to 72 Gy [with b.i.d. RT for last 12 fractions (1.8 and 1.5 Gy)]

Onupdate, 5-year LRF and DFS improved w/ HFX and CB vs.standard fx and split-course. LRF: 60% standard, 58% splitcourse,52% CB, 51% HFX. DFS: 21% standard, 27% splitcourse,29% CB, 31% HFX. No difference in DM (27-29%), CSS (40-46%). Trend for improved OS with HFX (37 vs.29-34%).

Altered fractionation (Bourhis 2006): Meta-analysis of 15 trials with 6,515 patients, 74% with stage III–IV disease, mostly of oropharynx and larynx, treated with conventional RT (1.8– 2/65–70 Gy), hyperfractionated RT (higher dose, same time), accelerated RT (same dose, shorter time), or accelerated RT with reduced total dose.

Altered fractionation improved 5-year OS by 3.4%, with greatest benefit for hyperfractionated RT (8% benefit) vs. accelerated RT (1.7–2% benefit). Five-year LRC benefit 6.4% overall, mainly for local as opposed to regional failure. Benefit highest for youngest patients (<50–60 years). No effect of altered fractionation on DM.

3.Chemo-RT ± altered fractionation

Adelstein, Intergroup (Adelstein et al. 2003):

295 patients with unresectable H&N cancer, randomized to 2/70 Gy vs. 2/70 Gy +cisplatin (100 mg/m2) ×3 cycles vs. split-course RT (2/30 Gy +2/30–40 Gy) + cisplatin/5-FU ×3 cycles.
Results: chemo-RT improved 3-year OS (23 vs. 37 vs. 27%) and DFS (33 vs. 51 vs.41%) but did not change DM and it increased toxicity

Bonner et al. (2006):

424 patients with locoregionally advanced resectable or unresectable stage III–IV SCC of oropharynx, larynx, or hypopharynx randomized to RT or RT + cetuximab given 1 week before RT and weekly during RT. RT options included 2/70 Gy, 1.2 b.i.d./72–76.8 Gy, or concomitant Boost 72 Gy.

Cetuximab increased 3-years LRC (34→47%) and OS (45→55%). With the exception of acneiform rash and infusion reactions with cetuximab, toxicity was similar.

MACH-NC meta analysis (Pignon et al. 2009):

93 phase III trials and 17,346 patients.
OS benefit (4.5%) at 5 years when chemotherapy was added to RT, with greater benefit for concurrent chemo-RT vs. induction chemo followed by RT (6.5% OS benefit with concurrent chemo-RT).
Similar results in trials with post-op RT, conventional, and altered fractionation. No difference between mono or polychemotherapy regimens, but increased benefit with platinum-based compounds.
Decreasing benefit with increasing age, with no benefit observed if more than 71-years old.

4. Post-op chemo-RT

EORTC 22931 (O'Sullivan et al. 2001, Cooper et al., NEJM 2004):

334 patients with operable stage III/IV H&N cancer randomized to post-op 2/66 Gy vs. post-op 2/66 Gy + concurrent cisplatin (100 mg/m2) on days 1, 22, and 43.

Chemo-RT improved 3/5-year DFS (41/36→59/47%), OS (49/40→65/53%), and 5-year LRC (69→82%).

No difference in DM (21–25%) or second primaries (12%).

Chemo-RT increased grade 3/4 toxicities (21→41%).

RTOG 91-11 (Forastiere et al. 2003; update *ASCO* 2006):

547 patients with stage III/IV larynx (T2-3 or low-volume T4 without gross cartilage destruction or >1 cm base of tongue invasion, or LN+) randomized to one of three arms: RT alone, chemo -> RT, or concurrent chemo-RT. RT was 2/70 Gy in all arms. Induction chemo was cisplatin/5-FU × 2c -> reassessment.
If progression or <PR, treated with laryngectomy and post-op RT. If PR/CR -> third cycle chemo -> RT.
Concurrent chemo was cisplatin × 3c. All patients with cN2 had neck dissection within 8 weeks after RT.

On update, concurrent chemo-RT improved 5-year larynx preservation (84%) vs. induction chemo (71%) and RT alone (66%), and LRC (69%) vs. induction chemo (55%) and RT alone (51%). Chemo reduced the rate of DM (13% concurrent, 14% induction vs. 22% RT alone) and improved DFS (39% with chemo vs. 27% with RT alone).

No difference in OS (55% concurrent, 59% induction, 54% RT alone)

thank you